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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/735,296	01/14/2000	Shu-Hsia Chen	6923-084	7224

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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/735,296	CHEN ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27,38,42,46,48,50,52,54,56,58,60,62,64,66,68,70 and 72-75* is/are pending in the application.

4a) Of the above claim(s) *27, 72-75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38, 42, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5/7/04* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/7/04 has been entered.

The amendment filed on 5/7/04 has been entered. Claims 39-41, 43-45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, and 71 have been canceled. Claims 72-75 are newly submitted.

Newly submitted claims 72-75 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 72-75 are drawn to an ex vivo gene therapy method for treating cancer comprising the steps of genetically modifying cells in vitro, and subsequently administering the modified cells to a subject (classified in class 424, subclass 93.21); whereas the originally elected invention is directed to administering a combination of two compounds to a subject, wherein the first compound is a nucleic acid encoding a cytokine such as IL-12, and the second compound is 4-1BB ligand (classified in class 514, subclass 44). The different inventions have different method steps, different search criteria, different classification,

and requires distinct technical considerations. The newly claimed invention would have been restricted if presented originally.

Since applicant has received several actions on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 72-75 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 27, 38, 42, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72-75 are pending, however, claims 27, and 72-75 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 38, 42, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70 are under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WRITTEN DESCRIPTION AND ENABLEMENT REQUIREMENT

The prior rejection of claims 26, 28-71 is withdrawm in view of the amendments.

ENABLEMENT REQUIREMENT

Claims 38, 42, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70 stand rejected for reasons of record and following.

In 5/17/04 response, applicants argue, "the specification provides a variety of routes for administration" and submitted Hirschowitz et al and Siders et al publications as support for administration from a site remote from the tumor.

The arguments have been fully considered but they are not persuasive for reasons of record and following.

It is noted that both *Hirschowitz* and *Siders* use an adenoviral vector for IL-12 delivery, although the references support a systemic delivery of adenoviral vector to lung tissue or liver, they do not support the full scope of the claims drawn to using *any* type of nucleic acid administered via *any* route. This is because adenovirus is known for its tissue tropism to epithelial cells of respiratory system such as lung and hepatocytes in the liver. For example, *Siders et al* (J Immunol 1998;160:5465-74) clearly teach they use intravenous route for adv-IL-12 "BECAUSE THE LIVER IS A PRIMARY SITE OF INFECTION AFTER I.V.-ADMINISTERED ADENVIRUS" (abstract). *Gregory et al* (US 6,093,567) teach "ADENOVIRUS HAS A NATURAL TROPISM FOR AIRWAY EPITHELIA. THEREFORE, ADENOVIRUS-BASED VECTORS ARE PARTICULARLY PREFERRED FOR RESPIRATORY GENE THERAPY APPLICATIONS" (Column 4, lines 17-20). On the other hand, *Worth et al* (Clin Cancer Res. 2000;6:3713-8) teach that administration of Adv-IL-12 intranasally found no expression in the liver (left column, page 3715). Apparently, the transgene expression is associated with the type of nucleic acid used and the routes of administration. To this end, it is noted that vectors, whether delivered systemically or locally in vivo have unpredictable efficacy in

infecting/transfecting the target cells/tissue and that it is further unpredictable whether the transfected cells will express a therapeutic level of the heterologous gene. The types of the vectors and the route of administration are relevant for enabling the claimed invention because each type of virus has different tissue tropism and each vector system have different efficiency in transducing different types of cells. *Robbins et al* (Pharmacol Ther 1998;80:35-47) teach that each type of vector system has its unique advantages and limitations, "RETROVIAL VECTORS CAN PERMANENTLY INTEGRATE INTO THE GENOME OF THE INFECTED CELL, BUT REQUIRE MITOTIC CELL DIVISION FOR TRANSDUCTION. ADENOVIRAL VECTORS CAN EFFICIENTLY DELIVER GENES TO A WIDE VARIETY OF DIVIDING AND NONDIVIDING CELL TYPES, BUT IMMUNE ELIMINATION OF INFECTED CELLS OFTEN LIMITS GENE EXPRESSION IN VIVO. HERPES SIMPLEX VIRUS CAN DELIVER LARGE AMOUNTS OF EXOGENOUS DNA; HOWEVER, CYTOTOXICITY AND MAINTENANCE OF TRANSGENE EXPRESSION REMAIN AS OBSTACLES. AAV ALSO INFECTS MANY NONDIVIDING AND DIVIDING CELL TYPES, BUT HAS LIMITED DNA CAPACITY" (abstract). *Robbins et al* go on to teach that non-viral vectors such as naked DNA and liposomes are inefficient in gene transfer to cell nucleus (Section 2, page 36). For *in vivo* cancer therapy in a patient, these are the factors have to be considered. *Verma et al* (Nature 1997;389;239-42) teach "THE USE OF VIRUSES IS A POWERFUL TECHNIQUE, BECAUSE MANY OF THEM HAVE EVOLVED A SPECIFIC MACHINERY TO DELIVER DNA TO CELLS. HOWEVER, HUMANS HAVE AN IMMUNE SYSTEM TO FIGHT OFF THE VIRUS, AND OUR ATTEMPTS TO DELIVER GENES IN VIRAL VECTORS HAVE BEEN CONFRONTED BY THESE HOST RESPONSE" (last paragraph of left column on page 239). *Miller et al* (1995, FASEB J., Vol. 9, pages 190-199), acknowledge various vector system available in the art, then teach, "NO SINGLE DELIVERY SYSTEM IS LIKELY TO BE UNIVERSALLY APPROPRIATE, FOR INSTANCE, THE REQUIREMENTS OF GENE

THERAPY FOR CYSTIC FIBROSIS ARE GREATLY DIFFERENT FROM THOSE OF CANCER" (1st paragraph, page 190). "ONCE AGAIN, TARGETING AT THE LEVEL OF THE VECTOR HAS NOT YET BEEN PARTICULARLY WELL DEVELOPED; HENCE, LIPOSOME OR VIRAL-MEDIATED DELIVERY OF THE CFTR GENE TO AIRWAY EPITHELIAL CELLS OF CF PATIENTS HAS RELIED LARGELY ON THE LOCALIZED DELIVERY OF THE VECTORS DIRECTLY TO THE AFFECTED TISSUES" (1st paragraph, page 198) Accordingly, for reasons of record such as taught by *Colombo et al* and *Caruso et al,* and those set forth *supra*, the specification fails to provide an enabling disclosure to support the full scope of the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Upon further search and consideration, previous rejections under this provision have been modified and appear below.

Claims 38, 42, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Caruso et al* (PNAS 1996;93:11302-6), taken with *Melero et al* (Nat Med 1997;3:682-5, IDS/CA), and *Kim et al* (Eur J Immunol 1998;28:881-90, IDS/DM).

Caruso et al teach a method for treating liver metastasis of colon cancer comprising administering intratumorally to a subject an effective amount of an

adenoviral vector encoding IL-12 in a mouse model, which leads to increased survival time of animals. *Caruso et al* go on to teach that IL-12 is known to enhance the cytolytic activity of NK cells, T cells, and macrophages and promotes cellular immune response by facilitating the proliferation and activation of Th1 cells. *Caruso et al* also teach that antitumor activity of IL-12 is mainly mediated by IFN-γ (left column, page 11304). The teaching of *Caruso et al* differs from instantly claimed invention in that they do not teach administering an effective amount of 4-1BB ligand in addition to the AdvIL-12.

Melero et al supplemented the teaching of *Caruso et al* by disclosing that antibodies against the 4-1BB (i.e. served as 4-1BB ligand) can eradicate established tumors. *Kim et al* supplemented the teachings of *Melero et al* by further elucidate the mechanism of action, i.e. 4-1BB signal promotes Th1 cell response, and enhance IFN-γ production.

Accordingly, the ordinary skilled artisan would have been motivated to combine the methods taught by *Caruso et al* and *Melero et al* by simply administering a 4-1BB ligand of *Melero et al* in addition to AdvIL-2 of *Caruso et al* for maximizing the tumor killing effect. Given that each of the cited references teaches an agent that is effective in cancer therapy, and shares a common mechanism of operation, a reasonable success and an enhanced benefit of cancer killing is expected. The instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to produce a third composition that is to be used for the very same purpose since the idea of

combining them flows logically from their having been individually taught in the prior art. Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art to combine these agents to generate a new composition for the treatment of cancer with a reasonable expectation of success.

In 5/7/04 response, Applicants submitted that unexpected results are provided in the specification, and cited MPEP § 716.02(a) to support the argument that the results are unexpected because the synergistic effect of the IL-12/4-1BB ligand combination is far greater than would be expected from the combination of two anti-cancer agents which act by increasing IFN-g secretion. Applicants also submitted a post-filing date publication showing that synergistic effect could reduce the effective dose of IL-12 up to 18-fold.

The arguments have been carefully considered but found not persuasive for reasons set forth *supra* and following.

As an initial matter, it is noted that there is no requirement on the dosage or effectiveness of IL-12 or 4-1BBL, thus, the combined teachings met claim limitation.

Concerning the unexpected results, it is noted that immediately following the passage cited by the applicants, MPEP further instructs, "HOWEVER, A GREATER THAN ADDITIVE EFFECT IS NOT NECESSARILY SUFFICIENT TO OVERCOME A PRIMA FACIE CASE OF OBVIOUSNESS BECAUSE SUCH AN EFFECT CAN EITHER BE EXPECTED OR UNEXPECTED. APPLICANTS MUST FURTHER SHOW THAT THE RESULTS WERE GREATER THA THOSE WHICH WOULD HAVE BEEN EXPECTED FROM THE PRIOR ART TO AN UNOBVIOUS EXTENT, AND THAT THE RESULTS ARE OF A SIGNIFICANT, PRACTICAL ADVANTAGE. *Ex parte The NutraSweet Co., 19 USPQ2d 1586.* (emphasis added). In the cited case law, evidence showing greater than additive

sweetness resulting from the claimed mixture of saccharin and L-aspartyl-phenylalanine was not sufficient to outweigh the evidence of obvious because the teachings of the prior art lead to a general expectation of greater than additive sweetening effects when using mixtures of synthetic sweeteners. In the instant case, assuming the dosage/response limitations were placed in the claims, the prior art of record consistently teach that both IL-12 and 4-1BB would enhance T cell response/IFN production significantly when used in a combined therapeutic regimen. For example, addition of IL-12 to an antigenic vaccine composition, the number of metastases reduced from 43% of controls to 15% of controls (*Hirschowitz et al*, e.g. abstract), while 4-1BBL increased CD28-mediated IFN-γ production by 7.3 times (*Kim et al*, table I). Thus, an 18-fold increase of effectiveness/decrease of dosage is reasonably expected when use the combination of IL-12 and 4-1BBL.

The prior rejection of Claims 40, 41, 43-45, 47, 49, 51, 53, 54-57, and 71 under 35 U.S.C. 103(a) as being unpatentable over *Caruso et al*, *Melero et al,* and *Vinay et al* as applied to claims 38, 39, 42, 46, 48, 50, 52, 54, 55, 58-67, and 70 above, and further in view of *Goodwin et al* (US 5,674,704), and *Deetz et al* (US 5,853,714), is withdrawn because the rejected claims have been canceled.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JANICE LI
PATENT EXAMINER

Q. Janice Li
Patent Examiner
Art Unit 1632

QL
July 19, 2004